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Dr. Joshua Lederberg
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Dear Dr. Lederberg:

Your Science and Man column in today's Washington Post startled and disappointed me. It is a piece of work unbecoming a man of your lustrous reputation. It is marked by an absence of careful factfinding, of precision and of relevance. I had hardly been prepared for a complaint in, of all places, The Washington Post, against "glib" newspaper accounts of the report made by the Advisory Committee on Obstetrics and Gynecology of the Food and Drug Administration. Anyone who attempts a serious discussion of the safety of the oral contraceptives does so at considerable peril, but if the condescending word "glib" should be affixed anywhere I suggest it might more appropriately be attached to publications other than The Washington Post, to Commissioner James L. Goddard of FDA, to Alan Guttmacher of Planned Parenthood and, regrettably, to Joshua Lederberg of Stanford, as well as to the Advisory Committee itself.

On August 15 the newspaper that publishes your column devoted more than a full page to stories related to the Committee report and to excerpts from that report. In the few days after that we carried a news analysis (Aug. 16), an editorial and a second, and lengthy, news analysis (Aug. 28). Perhaps you did not intend that the word "glib" apply to The Washington Post. Perhaps you did. In any event, you tarred everyone indiscriminately. I would think one could have expected from you some effort to distinguish between the performance of The Washington Post and that, say, of the Baltimore Sun, which on Aug. 15 printed not one word about the report; of Newsweek, Time and the AMA News, all of which carried false headlines asserting that the birth control pills had been found "safe"; of the New York Times and the Wall Street Journal, both of which said in their stories that the Committee had found no "evidence" the pills were unsafe (even Dr. Goddard made the same blooper. Of course there was "evidence"; what was at issue was the quantity and quality of the evidence). If you intended to brand the coverage given this matter by The Washington Post as "glib," then I invite you to say what your reasons are.

One error in several press accounts was attributable not to reporters, but to Dr. Goddard. Newspapers repeated - we did not, I am happy to say - his assertion, which was in a prepared statement distributed at a press briefing on August 11, that 20,000 women in the District of Columbia are in prospective studies sponsored by the National Institutes of Health in cooperation with D.C. Planned Parenthood. When I checked I found that such studies are nonexistent - that NIH has a contract to see if such studies are feasible, and that the contract is not with Planned Parenthood, but with the D.C. Department of Public Health. Who was being "glib"?

Whatever criticisms may be made of the Committee and its reports, no one can fairly say that there was not a predominant note of caution. Over and over, in regard to cancer, clotting, diabetes, effects on the offspring--over and over the theme was repeated that the data are insufficient, that more must be learned. One could not gather it from your reference to the "amber light," but the fact is that it was Dr. Hellman himself who, at the August 11 press briefing, characterized the report as "a yellow light of caution." Drug News Weekly went further and said the report was a yellow light or a red light. In a casual, almost flippant way, Dr. Goddard went on television to give what was, for practical purposes, a green light. Dr. Guttmacher said the report was "a complete green light." But in an appearance on Aug. 15 on National Educational Television Dr. Roy Hertz, a member of the Committee, said that any characterization of the report as a green light was "totally fallacious." Correct me if I'm wrong, but I suggest that if anyone was being "glib" it was Drs. Goddard&Guttmacher, not Drs. Hellman & Hertz; and that if one is going to criticize "glib" newspaper accounts permeated by "confusion and contradictions", one might put the blame where it belongs, on sources such as Drs. Goddard & Guttmacher.

You quoted the conclusion of the report, wherein is the crucial statement that the Committee "finds no adequate scientific data, at this time, proving these compounds unsafe..." I submit that one might have expected a scientist to make note of at least one of the following points:

*A statement of this kind is unscientific in that it fails to give the necessary counterbalance, that there is "no adequate scientific data, at this time, proving these compounds safe..."

*The Committee did take a scientific approach in the introduction to its report, when it said that there is such a paucity of data on severe adverse effects that "any assumptions"--I repeat, "any assumptions"--must be considered "unreliable."

*If the pills should ever be unsafe, which I emphatically hope they are not, this will never be "proved." There can be no proof in the legal sense, nor in matter of the public health can proof be awaited. You surely know, for instance, that no association between cigarette smoking and lung cancer, heart disease and other afflictions has been "proved." What we have, and what we may someday have in connection with the pill, is a statistical association. The probability that the pills cause clots, strokes, eye damage, or whatever, may be of a higher or lower order, and at certain rates. That is what our decisions will have to be based on.

In your next paragraph you quote the advice of the Committee that each physician must evaluate the advantages and the risks of the pills, and that he "can do this wisely only when there is presented to him dispassionate scientific knowledge of the available data." What you fail to do is to note the meagerness of such data and of the efforts to expand the body of knowledge to meaningful proportions.

Specifically: In 1963 the FDA's Wright Committee said the data available showed an incidence of fatal pulmonary embolisms in women taking Enovid of about 12 per million, compared with an incidence in the normal female populations of about 8 per million. The Committee sensibly concluded that the difference was statistically insignificant. But it also sensibly concluded that the data on nonfatal clots were hopelessly imprecise, that the data on fatal clots was shaky, that the pill insofar as fatal lung clots were concerned had not been demonstrated to be unsafe (or safe) and that a controlled, prospective study was needed. No such study has been done; FDA has failed to implement the recommendation. The Advisory Committee now, three years later, bemoans the situation and says we must have a retrospective study (in recommending against a prospective study for clotting while recommending for such a study of cancer, it cited "cost", which was not its business, and complexity). But, in any case, would it not have been appropriate for you to have noted the lack of data on clotting that now has been damned by two FDA Committees? Would it not have been appropriate for you to have noted that the latency period for human cancer is a decade, and that a physician does not have the means to detect it before then? And that the Committee emphasizes that it does not know whether the pills have, or do not have, a carcinogenic potential? Would it not have been appropriate for you to bring out the same fact--the fact of ignorance--as to effects on future offspring (see the special report by Dr. Hertz that the Committee included), on diabetes, on strokes, on infarctions, on masculinization of the fetus?

In column two of your article you engage in some statistical discussion that I find, frankly, atrocious, and this after dragging in the abortion chestnut. All we are (or should be) concerned with if there is to be a pretense to a scientific approach, it seems to me, is this question: Is there, or is there not, a higher risk of injury or death--and, if there is, how much higher--in women who use the pills than in women who use other forms of contraception? I am concerned about the problem of abortion, too, but I do not think it relevant to the need for getting the facts about the medical characteristics of the pill. Abortions have nothing in the world to do with whether the pill causes strokes. If, let's say, Ralph Nader wants to praise the Rover and condemn the Volkswagen, let him do so without dragging in the problem of drunken drivers. As to your statistical discussion: You wrote that "even today pregnancy carries a risk of 300 maternal deaths per million gestations. This number is at least 20 times higher than for any specific side effects that might conceivably be attributed to the pill by interprepation of the existing statistics."

Let us assume that there is indeed a risk of 300 maternal deaths in pregnancy. The maximum risk of clotting is acknowledged to be in the period immediately after pregnancy - acknowledged, incidentally, by the Committee in its report. As you note, the pill induces a pseudo pregnancy. But you and the Committee fail to note that a woman on the pill is in effect pregnant and delivering 13 times a year. She may, therefore, be running the maximal clotting risk 13 times as often as a nonuser. Is this not relevant? Let us go on. You said the 300-per-million rate "is at least 20 times higher than for any specific side effect..." Where is your authority for that? If--and it's a big if--there is in fact a 4 per million higher incidence in Enovid users than nonusers of fatal pulmonary embolisms (12 minus 8), the pregnancy risk is 80 times higher. But if you know what the risk may be of strokes, of nonfatal thromoboembolisms, of infarctions, of migraine, of psychic depression, of cancer, of foetal malformations--if you know what the rate is for any of these things, let alone for the sum of them, then, Sir, my hat is off to you, because you have informational sources denied the Advisory Committee, the FDA, the pill manufacturers, the medical journals and everyone else I know of.

But your statistical reasoning is atrocious for yet another reason. No one, to my knowledge, has suggested that a woman who uses a diaphragm and jelly runs a risk of cancer or stroke. FDA forms no committees to investigate the such a possibility. Assume that the efficacy of the pill is 100 per cent. The efficacy of the diaphragm, properly used, is about 98 per cent. It is,

therefore, a scientific and statistical fallacy to lay the death rate in pregnancy alongside a wholly conjectural death rate among users of the pill. Would you not agree that for those women who can properly use a diaphragm (for the sake of simplicity, I am leaving out the impressively efficacious use of foam alone, and of other mechanical contraception) the comparison should be made, if it is to be made at all, between in terms of the 2 per cent in whom contraception will fail? To put it another way: the fatal hazards of pregnancy you decry will be faced not by 5 million women who use a diaphragm in preference to a pill, but by 2 per cent of the 1 million, or 20,000. At the rate you cite, 300 per million, the hazards there exists for 6 women who will die--6 per million, and not, in those women using a diaphragm, the 300 you imply.

I want to turn now to some other points. The Washington Post's news coverage referred to the Advisory Committee neither as distinguished nor as undistinguished. Each of those adjectives is a loaded, judgmental word. You chose to call the Committee "distinguished." You would say, clearly, that "Lou" Hellman is "distinguished," because you praise "his temper and wisdom." I would, I suppose, say that Dr. Hertz could claim to be distinguished, because he is the former chief of endocrinology of the National Cancer Institute and, more recently, the former scientific director of the National Institute of Child Health and Human Development. But I would appreciate hearing from you what the makes the Committee, in your eyes, "distinguished." I was kind enough not to point out what should be apparent to a scientist, that the very name of the Advisory Committee on Obstetrics and Gynecology distinguishes the group from it from the balanced group one might expect--a group including representatives of the other specialities deeply involved in the questions presented by the pill, hematologists, to name but one. Another bit of knowledge counseling restraint in describing the Committee, but one you may be unaware of, is that some of the members were in the FDA-convened group that voted against a proposal to add a warning against use in women of childbearing age to the labels of over-the-counter products containing one of three antihistamines (cyclizine, chlorcyclizine and meclizine) suspected of causing birth a capability to cause foetal malformations. For reasons given in the foregoing, I did not find the conclusion of the Committee report distinguished in scientific terms. I found it troubling that the Committee could say that the pills require observance of an "unprecedented standard of safety," but recommend against a prospective clotting study on the grounds of cost and complexity; that it could recommend a retrospective trial that its chief advocate, Dr. Surtwell, concedes would not, even if fully implemented, detect one nonfatal clot in 4000 (or fewer) pill takers; that it could say that the

maximum clotting risk is immediately after pregnancy, but fail to say that pill users are taking pregnant 13 times a year; that it could publish a report from its task force on thromboembolic phenomena that omits a bibliography, while including a letter sent out in 1962 by G.D. Searle & Co., the manufacturer of Enovid, in the number of 275,000 copies.

You wrote that FDA's initial approval was given on "on the basis of experience with some few hundred or thousand women..." I will be precise if you will not. At the time Enovid was approved for birth control use by FDA the number of women in whom it had been tested for 12 to 21 consecutive menstrual cycles was 66; the number in whom it had been tested for 24 to a maximum of 38 consecutive menstrual cycles was another 66, for a grand total of 132, and the number of cases it had in hand, "properly documented with laboratory studies," as to cancer was 400. In the [redacted] literature today the number of women under 40 who have used the pill for a long time, and who have been adequately studied and reported is, according to Dr. Hertz, 85. I trust these figures shock you. They are shocking to, for example, Dr. Raymond Holden of Washington. He headed the AMA's Committee on Human Reproduction and Fertility. After the AMA Committee's report on contraception appeared in the Journal of the AMA last October I discussed with Dr. Holden the striking lack of emphasis in the report on the pill on safety, the question being dismissed there with the statement that safety had been assured by FDA. He was shocked to learn that only 132 women had received Enovid for a maximum of 38 consecutive menstrual cycles. His Committee - a professional source of information for physicians - did not know of the 132 figure, which was published by a Senate subcommittee early in 1963 and was cited in, among other places, my book, The Therapeutic Nightmare. Referring to the figure of 132, Dr. Holden said to me, "You know that's not enough." I know it. Do you?

I do not understand why you think the prime need now is to "scrutinize the available data..." The trouble with the available data is clearly that it is full of holes, and that it does not lend itself to fine analysis. Are you joining in opposition to a prospective clotting study, even though the FDA's Wright Committee (was it less "distinguished" than Dr. Hellman's Committee?) urged such a study, and even though it has been urged anew by Dr. Hertz?

I am sure that if I had taken more time I would have been more pointed and more coherent. But I thought it important to deal with this at once. I have, regrettably, a tendency to react strongly to nonscience proferred by a scientist with credentials as distinguished as yours.

Sincerely yours,
Morton Mintz

The Washington Post
Morton Mintz, National Reporter